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DEVELOPMENT OF TERMOGRAVIMETRIC METHOD FOR QUANTITATIVE DETERMINATION OF KETOCONAZOLE

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The objective of this work was to develop and validate a fast and reproducible method which is able to determine the concentration of ketoconazole in raw materials and tablets. The samples were analyzed by dynamic thermogravimetry at heating rates of 10, 20, 40, 60 and 80°C min^{-1} in nitrogen and nitrogen-synthetic air mixture. The concentrations of ketoconazole in the raw material and in the tablets were obtained from the vapor pressure curves. The data showed that there is no significant difference between the vapor pressure profiles of ketoconazole itself and in its tablet in both studied environmental conditions confirming that the process is really vaporization. The concentration of ketoconazole was determined in the raw material and tablets of the drug.

Keywords: *Antoine equation, ketoconazole, Langmuir equation, thermogravimetry, vapor pressure*

Introduction

Ketoconazole is an imidazolic antifungical derivative which is a potent non-selective inhibitor in the steroid synthesis of the adrenal glands and gonads [1].

Thermoanalytical techniques can be used for several purposes in pharmaceutical technology, e.g. for thermal characterization [2–5], stability [6–10] and preformulation studies [11, 12], as well kinetic and thermodynamic analysis [13, 14].

Some years ago attempts were done to develop and validate methods to measure the vapor pressure of substances [15–17].

In order to determine the vaporization processes of substances the behavior of the analysed sample should follow a zero order kinetic reaction [18].

The objective of this work was to develop a fast and sensible method for quantitative analysis of ketoconazole using thermogravimetry based on the vapor pressure determination of the drug.

Experimental

Materials and methods

Methylparaben (reference), pure ketoconazole and its tablets containing 200 mg of active compound were used in this study. Calorimetric curves of methylparaben (reference), pure ketoconazole and its respective product were recorded using a Shimadzu DSC-50 calorimeter in nitrogen (flow rate: 50 mL min^{-1}) at different heating rates (10, 20, 40, 60 and 80°C min^{-1}) up to 500°C. Non-isothermal thermogravimetric curves of pure ketoconazole and tablets of 200 mg were obtained using a Shimadzu TGA-50H thermobalance applying 10, 20, 40, 60 and 80°C min^{-1} heating rates up to 900°C (in three replicates) in synthetic air (at a flow rate of 20 mL min^{-1}) and flowing nitrogen (50 mL min^{-1}). Non-isothermal thermogravimetric curves of methylparaben were recorded using the same Shimadzu thermobalance and also in the same heating rate up to 400°C, when the process of mass loss finished (three parallel runs were recorded). The initial sample mass was 8.0±0.5 mg, which was put in an alumina crucible. Curves were analyzed by TASYS program from Shimadzu, to characterize the mass loss stages. The samples were analyzed in two environmental conditions: besides nitrogen, synthetic air as oxidative atmosphere was used. The objective of this study was to verify the vaporization process of ketoconazole and starting from this fact to determine the tension curves profiles.

Quantitative determination of ketoconazole

Curve patterns of ketoconazole drug diluted with microcrystalline cellulose were prepared in the rate of 20°C min^{-1}, in the following proportions of ketoconazole:microcrystalline cellulose: 160:120, 180:100, 200:80, 220:60 and 240:40, in nitrogen and nitrogen with synthetic air. The raw material and the

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ketoconazole tablets were analyzed by the calibration curve, using the straight line equation.

Kinetic study

Arrhenius equation

Non-isotherm thermogravimetric data were used to determine the reaction order by Arrhenius equation [19].

$$k_{vap} = A e^{-E_{vap}/RT}$$

where, E_{vap} is the vaporization energy, A is the preexponential factor, R is the universal gas constant, T is the absolute temperature and k_{vap} is the evaporation coefficient.

Antoine equation and Langmuir equation

Data obtained from thermogravimetric experiments of methylparaben were used to construct the vapor pressure curves, using the Antoine equation and after determining the value of '*k*', which was used to construct the vapor pressure curves of drug and tablets of ketoconazole, using the Langmuir equation.

The Antoine's equation [19] is presented as:

$$\ln P = \frac{A-B}{T+C}$$

where P the vapor pressure, T is the absolute temperature and A, B and C are the Antoine's constants in the studied temperature interval [20]. Antoine constants for methylparaben are: A=5.23662, B=1159.34 and C=–220.03, in the 446–517 K temperature interval [20].

The Langmuir equation [19] is:

$$dm/dt = P\alpha (M/2\pi RT)^{1/2}$$

where (dm/dt) is the rate of mass loss per area unit, P is the vapor pressure, α is the vaporization constant and M is the molecular mass of the evaporated vapor.

The Langmuir equation can be modified to obtain the vapor pressure values of many simple components. The following modification is described [19]:

$$P = [\alpha^{-1}(2\pi R)^{1/2}][(T/M)^{1/2}(dm/dt) = k\upsilon$$

where, $k=\alpha^{-1}(2\pi R)^{1/2}$ and $\upsilon=(T/M)^{1/2}(dm/dt)$.

If k is constant, t a group of data and it is independent of the used material, so the graphic of P *vs*. υ gives the value of k.

Ozawa method

Activation energy based on the non-isothermal TG curves of pure drug and tablet was determined using the Ozawa method [21]:

$$\frac{d\alpha}{f(\alpha)} = \frac{A}{\beta}\exp\left(\frac{-E}{RT}\right)dT$$

where α=degree of conversion, $f(\alpha)$=kinetic model, A=preexponential factor, T=temperature in K, R=universal gas constant, β=heating rate, E=activation energy.

f_1 and f_2 equations

f_1 and f_2 equations are recommended by FDA as an acceptable method to compare the dissolution profiles. However, this method was used because it compares straight lines parallel bars, in which f_1 defines the difference between the straight lines and f_2 defines the similarity between them. Data from vapor pressure curve profiles of the drug and of the ketoconazole tablet in both environmental conditions were used in the f_1 and f_2 equations.

The difference factor (f_1) calculates the f_1 percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum 2 of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

The acceptance limits for two samples belonging to the same population are: f_1 smaller than 15% and f_2 bigger than 50% [22].

$$f_1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right\}100\%$$

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5}100\right\}$$

Results and discussion

Calorimetric characterization of drug and tablets of ketoconazole

Pure drug and ketoconazole tables presented two transition phases. The first endotherm refers to the fusion of the drug and the second, exothermic transition refers to the volatilization process that may be confirmed by the thermogravimetric experiments. The onset fusion temperature of the ketoconazole drug at 10°C min^{-1} heating rate was 147.4°C, as cited in the literature [23], accompanied by of 80.7 J g^{-1} heat effect and onset decomposition of 363.0°C and reaction heat of 27.3 J g^{-1} at the same heating rate. However, ketoconazole tablet presents an endotherm and

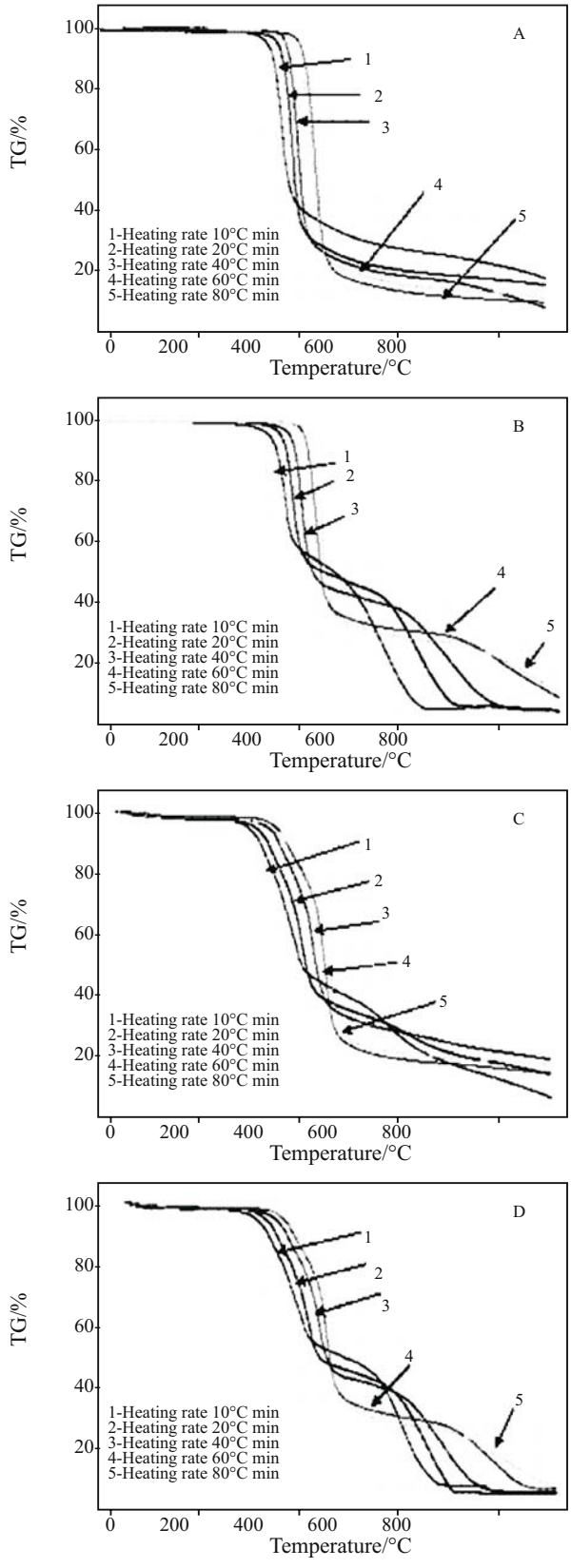

Fig. 1 TG curves A – ketoconazole drug in nitrogen and B – nitrogen with synthetic air and C – ketoconazole tablet in nitrogen and D – nitrogen with synthetic air at different heating rates

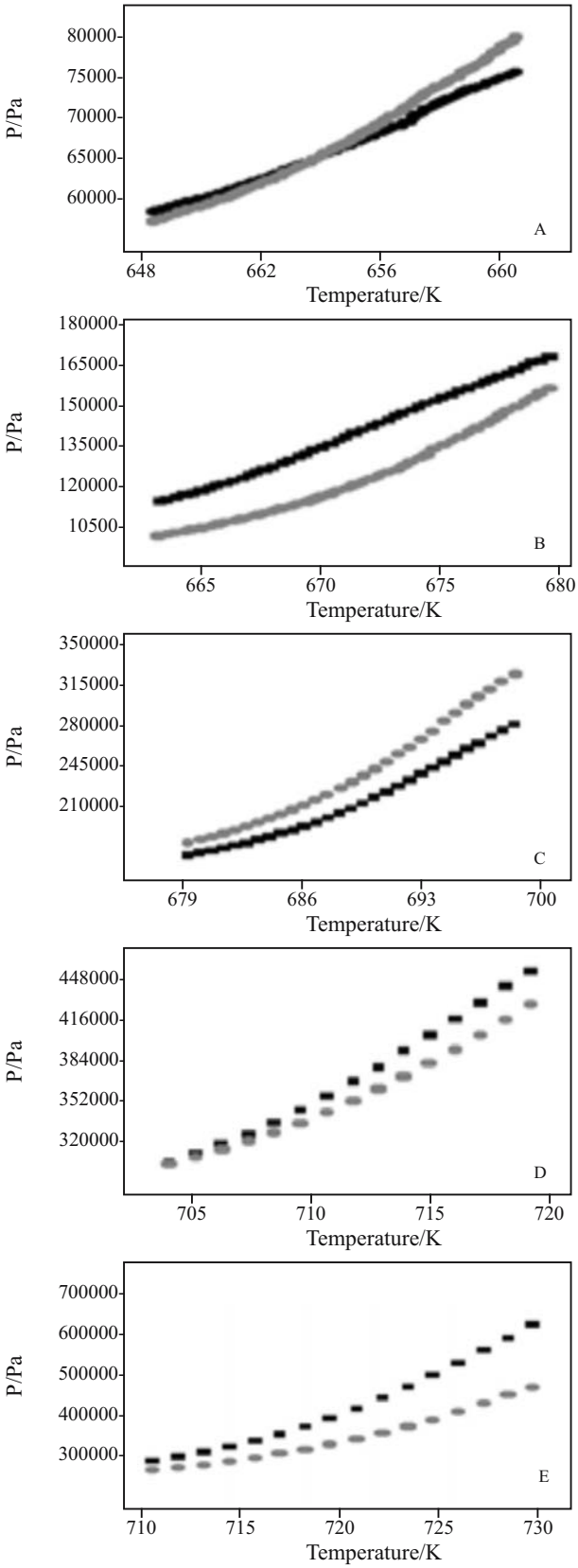

Fig. 2 Pressure curves of ketoconazole tablet at heating rates of: A – 10, B – 20, C – 40, D – 60 and E – 80°C min^{-1} in ■ – nitrogen and ■ – in nitrogen–synthetic air

Table 1 f_1 and f_2 data for ketoconazole drug and tablet as the result of the comparison of the vapor pressure profiles in nitrogen and in nitrogen-synthetic air mixture at various heating rates

Ketoconazole drug									
10°C min^{-1}		20°C min^{-1}		40°C min^{-1}		60°C min^{-1}		80°C min^{-1}	
f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2
2.84	61.98	9.58	103.63	4.42	96.83	1.39	82.23	5.61	115.18
2.63	60.73	10.09	105.44	4.58	97.91	1.22	80.13	6.38	118.77
2.26	58.26	10.89	108.02	4.83	99.54	1.71	89.96	7.34	122.85
1.99	56.27	11.42	109.92	5.11	101.29	2.36	99.14	7.78	124.91
1.60	53.87	11.25	110.30	5.45	103.29	3.01	105.72	8.87	129.65
1.41	52.14	10.66	109.85	5.83	105.62	3.42	109.09	10.22	135.01
Ketoconazole tablet									
10°C min^{-1}		20°C min^{-1}		40°C min^{-1}		60°C min^{-1}		80°C min^{-1}	
f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2
5.98	73.25	9.17	97.60	10.37	112.36	1.68	81.96	0.37	53.57
6.04	74.07	9.26	98.42	10.44	112.97	1.65	82.21	0.48	60.40
6.10	74.94	9.14	98.76	10.43	113.44	1.62	82.24	0.58	65.40
6.11	75.65	9.09	99.28	10.41	113.89	1.56	81.99	0.72	71.46
6.10	76.36	9.09	100.05	10.48	114.60	1.46	81.24	0.85	75.98
6.11	77.27	9.08	100.85	10.53	115.32	1.30	79.77	1.01	80.91

exotherm effect at 142.3°C and 357.7°C, respectively suggesting an interaction between the drug and any formulation component, which can be identified and confirmed later.

Thermogravimetric characterization of drug and tablets of ketoconazole

TG curves of ketoconazole in nitrogen (Fig. 1A) and in nitrogen–syntetic air mixture (Fig. 1B), presented two thermal decomposition stages. The corresponding mass losses at 10°C min^{-1} heating rate were approximately 43%. This loss enhances up to 68% as the heating rate reaches 80°C min^{-1} heating rate. Similar behavior was observed for ketoconazole in nitrogen for the first mass loss stage. In mixed atmosphere for the second TG stage (Fig. 1B) 56% mass loss was observed for 10°C min^{-1} for heating rate which shows decreasing tendency by the increasing of the heating rate (27% mass loss was observed when the heating rate was 80°C min^{-1}). In nitrogen (Fig. 1A) the mass loss varied from 13 to 7.5% while the heating rate increased from 10 to 80°C min^{-1}. The data of the second stage showed that ketoconazole undergoes thermal decomposition instead of volatilization in this temperature range since differences in the mass losses were found in the two used atmospheres.

The ketoconazole tablet in nitrogen (Fig. 1C) and nitrogen with synthetic air (Fig. 1D) showed three-step of thermal decomposition at *a* heating rates of 10, 20 and 40°C min^{-1}. The first decomposition stage refers to the humidity loss up to about 96°C. In the second stage depending on the used atmosphere, approximately 45% in nitrogen–synthetic air (Fig. 1D) and 48% in nitrogen (Fig. 1C) were observed. At 60 and 80°C min^{-1} heating rates in both purging conditions only two decomposition stages were recorded. In the first stage started around 287°C in nitrogen and around 299°C in a nitrogen–synthetic air.

Determination of the reaction order, activation energy and respective pressure curves of ketoconazole drug and tablets

Methylparaben was used to calibrate the system presented zero order kinetics, which is according to the literature [24] is evaporization. The '*k*' value obtained to methylparaben at 10, 20, 40, 60 and 80°C min^{-1} heating rates in synthetic air was 125555, 245191, 414034, 605841 and 714416, respectively. In inert atmosphere at 10, 20, 40, 60 and 80°C min^{-1} heating rates the respective '*k*' values are 125413, 246932, 413676, 597515 and 709030. The activation energy for ketoconazole obtained by Ozawa method in nitrogen and nitrogen with synthetic air were respectively 121±1 (383–430°C) kJ mol^{-1} and 110±2 (335–400°C) kJ mol^{-1}. The activation energy for ketoconazole tablet in nitrogen and nitrogen with synthetic air were respectively 112±8 (270–400°C) kJ mol^{-1} and 112±5 (257–390°C) kJ mol^{-1}.

Ketoconazole drug and tablet also presented zero order kinetic reaction, which confirms a vaporization process. The '*k*' values of methylparaben were used to obtain the pressure values and the respective curves for the drug and tablet of ketoconazole in nitrogen and nitrogen with synthetic air at 10, 20, 40, 60 and 80°C min^{-1} heating rates (Figs 2 and 3).

Figures 2 and 3 shows that the vapor pressure increases with the increase of heating rate, however, it is worth to say that the vapor pressure for the drug is higher than for the ketoconazole tablet in both environmental conditions at all heating rates.

Table 1 shows the f_1 and f_2 values for the pure drug and ketoconazole tablet in both environmental conditions. The data showed that the values obtained for f_1 and f_2 are between the accepted limits at all heating rates, in other words, f_1 smaller than 15% and f_2 higher than 50%. Therefore, the results showed that there is no difference in the behaviour between the drug and the ketoconazole tablet in both environment conditions, confirming the mass loss process is volatilization.

Determination of ketoconazole content in tablets

Average pressure data of ketoconazole drug and tablet at 10, 20, 40, 60 and 80°C min^{-1} heating rates and in both environmental conditions were analyzed to obtain a factor. This factor was used as an analytical parameter in the selection of the most appropriate heating rate to describe the method, which was 40°C min^{-1}. It was obtained from a calibration curve in nitrogen and in nitrogen-synthetic air environment by linear regression: $314589.89+(-536.51)x$ and $R=0.9951$, $y=290570.82+(-403.92)x$ and $R=0.9988$. By using the calibration curve the concentration of ketoconazole in the tablet was 98.2% in nitrogen and 101.4% in nitrogen-synthetic air mixture. The obtained values are according to the American Pharmacopoeia, which is between 90 and 110%.

Conclusions

Data analysis showed that ketoconazole presented the same vapor pressure constants in the two different atmospheres (nitrogen and nitrogen with synthetic air). Ketoconazole drug was determined quantitatively in tablets by TG method.

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